INJECTABLE 2,6-DIISOPROPYLPHENOL-CONTAINING ANESTHETIC COMPOSITION AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

BACKGROUND OF THE INVENTION

This invention relates to a pharmaceutical composition, which is parenterally injectable in humans or animals, for inducing or maintaining anesthesia. More particularly, the invention relates to an injectable anesthetic composition in an aqueous phase comprising 2,6-diisopropylphenol (i.e., propofol) as an active ingredient.

2,6-Diisopropyl phenol, which is used as an anesthetic, has a lipophilic character and is thus able to easily penetrate the blood-brain barrier. Owing to its lipophilic character, 2,6-diisopropylphenol is water-insoluble, which has resulted in difficulty in developing a formulation for intravenous injection.

At present, an injectable formulation comprising propofol emulsified with soybean oil, phospholipid, and glycerin is commercially available from AstraZeneca. This injectable emulsion is problematic because its milky appearance makes it difficult to detect impurities with the naked eye. Further, the relatively large particle size (>100 μm) can lead to formation of

thrombi in capillaries and peripheral blood vessels.

U.S. Patent Nos. 4,056,635 and 4,798,846 disclose pharmaceutical compositions for general anesthesia, which are parenterally administrable to humans or animals, comprising a surfactant, such as CREMOPHOR EL or polysorbate 80 (TWEEN 80), and water-immiscible solvents, such as ethyl oleate or castor oil, and an additional solvent, such as ethanol, polyethylene glycol, or propylene glycol. These pharmaceutical compositions, however, have significant drawbacks in terms of causing adverse effects, and hypersensitive responses against CREMOPHORS can be induced in animals or humans.

Use of polysorbate 80 as a surfactant is disclosed in International Publication No. WO97/10814, however, the problem of hypersensitivity is also found in anesthetics containing polysorbate 80.

Thus, while prior art propofol-containing products and methods of use thereof are known and are generally suitable for their limited purposes, they possess certain inherent deficiencies that detract from their overall utility for anesthesia. In view of the foregoing, it will be appreciated that providing an injectable propofol -containing anesthetic composition that is optically clear and does not produce a hypersensitive reaction would be a significant advancement in the art.

BRIEF SUMMARY OF THE INVENTION

It is an advantage of the present invention to provide an injectable anesthetic composition that does not induce a hypersensitive reaction.

It is another advantage of the invention to provide an optically clear injectable anesthetic

composition that facilitates the detection of impurities or foreign matter contained therein with the naked eye.

In an illustrative embodiment of the invention, an injectable anesthetic composition comprises a microemulsion comprising a mixture of 2,6-diisopropylphenol, polyethylene glycol 660 hydroxystearate, tetrahydrofurfuryl alcohol polyethyleneglycol ether, and an aqueous medium. The composition can further comprise a surfactant selected from the group consisting of bile salts, lecithin, and mixtures thereof. Illustratively, the surfactant is present in an amount of about 0.1 to 0.5% by weight. In another illustrative embodiment of the invention, the aqueous medium comprises a tonicity adjustment agent in an amount sufficient to obtain an isotonic condition corresponding to blood plasma. Illustrative tonicity adjustment agents include trehalose, glucose, fructose, glycerol, sorbitol, mannitol, sucrose, xylitol, sodium chloride, and the like, and mixtures thereof. In certain illustrative embodiments of the invention, the composition comprises about 1 to 2% by weight of 2,6-diisopropylphenol, about 5 to 10% by weight of polyethylene glycol 660 hydroxystearate, about 10 to 25% by weight of tetrahydrofurfuryl alcohol polyethyleneglycol ether, and about 63-84% by weight of the aqueous medium.

Another illustrative embodiment of the invention relates to a method of making an injectable anesthetic composition comprising:

(a) mixing polyethylene glycol 660 hydroxystearate with the aqueous medium to result in an aqueous mixture and heating and then cooling the aqueous mixture to room temperature to result in an aqueous solution;

(b) adding 2,6-diisopropylphenol to tetrahydrofurfuryl alcohol polyethyleneglycol

ether to result in an oil-phase mixture and heating and then cooling the oil-phase mixture to room temperature to result in an oil-phase solution;

(c) mixing the aqueous solution and the oil-phase solution with stirring to result in a stirred mixture; and

(d) heating the stirred mixture with additional stirring and then cooling to room temperature to result in a microemulsion, thereby resulting in the injectable anesthetic composition.

Still another illustrative embodiment of the invention relates to a method for anesthetizing an animal or human comprising injecting the animal or human with an amount of an anesthetic composition effective for inducing or maintaining anesthesia, wherein the composition comprises a microemulsion comprising a mixture of 2,6-diisopropylphenol, polyethylene glycol 660 hydroxystearate, tetrahydrofurfuryl alcohol polyethyleneglycol ether, and an aqueous medium.

DETAILED DESCRIPTION

Before the present injectable anesthetic composition and methods of making and methods of use thereof are disclosed and described, it is to be understood that this invention is not limited to the particular configurations, process steps, and materials disclosed herein as such configurations, process steps, and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

The publications and other reference materials referred to herein to describe the background of the invention and to provide additional details regarding its practice are hereby incorporated by reference. The references discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to an anesthetic composition comprising "a surfactant" includes a mixture of one or more of such surfactants, reference to "an aqueous medium" includes reference to two or more of such aqueous media, and reference to "the thickening agent" includes reference to a mixture of two or more of such thickening agents.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

As used herein, "comprising," "including," "containing," "characterized by," and grammatical equivalents thereof are inclusive or open-ended terms that do not exclude additional, unrecited elements or method steps. "Comprising" is to be interpreted as including the more restrictive terms "consisting of" and "consisting essentially of."

As used herein, "consisting of" and grammatical equivalents thereof exclude any element, step, or ingredient not specified in the claim.

As used herein, "consisting essentially of" and grammatical equivalents thereof limit the scope of a claim to the specified materials or steps and those that do not materially affect the

basic and novel characteristic or characteristics of the claimed invention.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

As used herein, "aqueous medium" means a water-containing liquid, which may also contain salts, buffers, pH-adjusting agents, tonicity adjustment agents, and the like.

As used herein, "bile salts" are pharmaceutically acceptable salts of cholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid, ursocholic acid, ursodeoxycholic acid, isoursodeoxycholic acid, lagodeoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid, glycochenodeoxycholic acid, dehydrocholic acid, hyocholic acid, hyodeoxycholic acid, and the like, and mixtures thereof.

As used herein, "optically clear" and similar terms mean that the composition exhibits a transmittance at 660 nm of greater than about 90%, typically greater than about 94%, and more typically greater than about 97%.

As used herein, "PBS" means phosphate buffered saline, i.e., 0.01 M Na_2HPO_4, 0.15 M NaCl, pH 7.2.

Since the anesthetic composition of the present invention is intended to be administered to a warm-blooded animal, including humans, the ingredients should be pharmaceutically acceptable for administration to animals and humans.

The present invention is directed to an injectable anesthetic composition comprising a microemulsion comprising 2,6-diisopropylphenol as an active ingredient and the hydrophilic surfactant, polyethylene glycol 660 hydroxystearate (CAS No. 70142-34-6), and the cosurfactant and cosolvent, tetrahydrofurfuryl alcohol polyethyleneglycol ether (CAS No. 31692-85-0), wherein the microemulsion is formed by mixing these ingredients with an aqueous medium.

2,6-Diisopropylphenol, which is a widely used injectable anesthetic, is typically added to pharmaceutical compositions in an amount of about 1-2% by weight for use in general anesthesia. If 2,6-diisopropylphenol is added in an amount of less that about 1% by weight, sufficient anesthesia may not be achieved, in animal or human subjects. If the added amount of 2,6-diisopropylphenol exceeds about 2% by weight, then adverse effects may occur owing to overdosing of the anesthetic agent.

Used in the present invention as a surfactant, polyethylene glycol 660 hydroxystearate is commercially available as SOLUTOL (BASF). For example, the product known as SOLUTOL HS 15 is known and commercially available.

In an illustrative embodiment of the invention, the surfactant polyethylene glycol 660 hydroxystearate is illustratively contained in the injectable anesthetic agent in an amount of about 5-10% by weight, but its content is not limited to this range. That is, it is possible for the surfactant to be added in an amount of less than 5% or more than 10%. However, taking into consideration the range of content of the active ingredient, 2,6-diisopropylphenol, the content of the surfactant is typically greater than 5%. In addition, in the presence of 2,6-diisopropylphenol added in a maximum amount of about 2% by weight, the surfactant displays good solubility even when added in an amount of 10% by weight.

Another additive, tetrahydrofurfuryl alcohol polyethyleneglycol ether is also commercially available as GLYCOFUROL (GF), which is exemplified as GLYCOFUROL 75.

In a typical embodiment of the present invention, the cosurfactant and cosolvent, tetrahydrofurfuryl alcohol polyethylene glycol ether, which acts as an auxiliary agent for dissolution of the active ingredient, 1,6-diisopropylphenol, is contained in the injectable anesthetic in an amount of about 10-25% by weight, but its content is not limited to this range. When the amounts of the active ingredient, 2,6-diisopropylphenol, and the major surfactant, polyethylene glycol 660 hydroxystearate, are within the ranges as described above, an amount of the auxiliary agent, tetrahydrofurfuryl alcohol polyethyleneglycol ether within the described range is sufficient to obtain a clear injectable aqueous solution.

If desired, the injectable anesthetic agent according to the present invention can further include other surfactants, including a bile salt, such as sodium deoxycholate, and lecithin, and such selection of surfactants can be easily determined by one of ordinary skill in the art. Illustrative amounts of the bile salt and lecithin are in the range of about 0.1-0.5% by weight.

Dispersion medium, which is an aqueous medium, may be pharmaceutically acceptable distilled water for parenteral injection or an aqueous solution prepared by adding a suitable amount of a tonicity adjustment agent to distilled water to give an isotonic condition. To maintain the isotonic condition, osmolality is about 200-900 mOsmol/kg, and typically, about 260-390 mOsmol/kg. Examples of the tonicity adjustment agent may include trehalose, glucose, fructose, glycerol, sorbitol, mannitol, sucrose, xylitol, sodium chloride, and the like, and mixtures thereof.

Besides the above ingredients, additives commonly used in the art may be used in the

present invention. For example, the injectable anesthetic agent may include a liquid excipient, which is exemplified as ethanol, propylene glycol, glycerol, triethylene glycol, polyethylene glycol, and mixtures thereof. Also, a pH regulator may be used to adjust the pH in the range of about 5.5 to about 9.5, and examples of pH regulators include citric acid, acetate, phosphoric acid, ascorbic acid, gluconic acid, succinic acid, tartaric acid, lactic acid, and the like, and salts thereof, and mixtures thereof.

In addition, the injectable anesthetic agent may further include any of the following additives in a pharmaceutically acceptable amount: a thickening agent, an absorbent, a light stabilizer, a crystallization inhibitor, a complexing agent, an antioxidant, and an antiseptic. Illustrative thickening agents include methylcellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, and mixtures thereof. Illustrative complexing agents include EDTA and salts thereof, phosphate, nitrate, acetate, citrate, and mixtures thereof. Illustrative antioxidants include ascorbic acid, sulfate compounds, L-cysteine, thiodipropionic acid, thiolactic acid, monothioglycerol, propyl galate, and mixtures thereof. Illustrative antiseptics include methyl *p*-oxybenzoate, propyl *p*-oxybenzoate, PHB ester, chlorobutanol, benzyl alcohol, butanol, butane-1,3-diol, chlorohexidin salts, benzoic acid and its salts, sorbic acid, and mixtures thereof.

The injectable anesthetic agent of a microemulsion type comprising the above ingredients according to the present invention illustratively and typically has a particle size of about 15-35 nm.

In accordance with the present invention, there is provided a method of preparing such an injectable anesthetic composition containing 2,6-diisopropylphenol (generic name: propofol) as

an active ingredient, which is homogeneously dispersed in an aqueous medium to give a clear emulsion, comprising (1) dissolving Solutol in an aqueous medium by adding it to distilled water for parenteral injection or an aqueous solution containing a tonicity adjustment agent and heating, for example to 40-80°C or more typically 50-70°C, and then cooling the resulting mixture to room temperature to give an aqueous solution; (2) adding an effective amount of propofol to GLYCOFUROL commonly used in an injectable preparation, heating to 40-80°C or more typically 50-70°C with stirring, and then cooling the resulting mixture to room temperature to give an oil-phase solution; (3) adding a suitable amount of the oil-phase solution into the aqueous solution at room temperature and then mixing the combination with stirring to allow reactions between the compounds; and (4) heating the reaction mixture again, illustratively at 40-80°C and more typically at 50-70°C with stirring, and then cooling to room temperature. Step 4 is usually repeated three or more times to produce a clear microemulsion.

Since a microemulsion is easily formed just by mixing with stirring according to the method of the present invention, the injectable anesthetic composition of a clear emulsion type according to the present invention can be simply prepared without use of high-cost equipment, such as a homogenizer or a microfluidizer, which are commonly used in the art.

The present invention will be explained in more detail with reference to the following examples in conjunction with the accompanying drawings. However, the following examples are provided only to illustrate the present invention, and the present invention is not limited by them.

As described above, the presently described injectable anesthetic composition does not induce hypersensitivity in animals or humans, and is optically clear, allowing detection of impurities with the naked eye, thus making it possible to prevent adverse effects from such

impurities.

Example 1

First, 7.5 g of Solutol HS 15 (BASF) was added to 50 ml distilled water for parenteral injection, and the mixture was heated at 60°C to dissolve Solutol HS in the aqueous medium, and the resulting mixture was then cooled to room temperature to give an aqueous solution. Separately, 15 g of Glycofurol 75 (commercially available from GF) was mixed with 1 g of propofol with heating, and the resulting mixture was then cooled to room temperature to give an oil-phase solution. The oil-phase solution was added to the water-phase solution little by little with stirring at room temperature. After the addition was ended, the mixture was well mixed with stirring at about 50 to 80°C, and then cooled to room temperature. The agitation at 50-80°C and cooling steps were performed three additional times, resulting in formation of a clear microemulsion.

Thereafter, about 26.5 ml of 1/15 M phosphate buffered saline (pH 7.4) was added to the microemulsion, thus giving 100 ml of a 1% injectable preparation, which contains propofol in an amount of 1% by weight.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity, pH, particle size, and zeta-potential, and the results are give in Table 1.

Example 2

To investigate the effects of the drug propofol on the physical and chemical properties of

injectable preparations when the amount of propofol is increased, another injectable preparation was prepared according to the same procedure as in Example 1, except for addition of 1.1 g propofol, and production of an injectable preparation of total volume of 110 ml, by addition of 10 ml more distilled water.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity, pH, particle size, and zeta-potential, and the results are set out in Table 1.

Example 3

An injectable preparation was prepared according to the same procedure as in Example 1, except for use of a 10% dextrose solution as the aqueous medium.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity, pH, particle size, and zeta-potential, and the results are give in Table 1.

Example 4

An injectable preparation was prepared according to the same procedure as in Example 2, except for use of a 10% dextrose solution as an aqueous medium.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity, pH, particle size, and zeta-potential, and the results are give in Table 1.

Table 1. Transmittance, pH, particle size, and zeta-potentials of injectable preparations in Examples 1 to 4.					
Preparation	Transmittance (%)		pH	Particle size (nm)	Zeta-potential (mV)
	540 nm	660 nm			
Example 1	96.1	97.75	7.71	16.7	-2.41~-2.56
Example 2	95.35	97.12	7.71	17.5	-3.85~-4.18
Example 3	97.05	98.51	7.60	16.5	-4.02~-4.05
Example 4	96.86	98.53	7.63	16.9	-2.27~-2.88

Examples 5-8

First, 7.5 g of Solutol HS 1 (BASF) was added to 50 ml of a 10% dextrose solution, and the mixture was heated to 50 to 80°C to dissolve the Solutol HS 15 in the aqueous medium. The resulting mixture was then cooled to room temperature to give an aqueous solution. Separately, 15 g of Glycofurol 75 (GF) was mixed with 250 mg of a bile salt (sodium deoxycholate) and 500 mg of 99% egg lecithin, and the mixture was heated at 50-80°C to dissolve the ingredients. Next, 1 g (Example 5), 1.1 g(Example 6), 1.2 g (Example 7), or 1.3 g (Example 8) of propofol was added to the resulting mixture and dissolved completely, thus giving an oil-phase solution. The oil-phase solution was added to the aqueous solution little by little with stirring at room temperature, and the resulting mixture was heated at 60°C for 5 minutes with agitation and then cooled to room temperature. The agitation at 60°C and cooling steps were repeated three more times, resulting information of a clear microemulsion.

Thereafter, 25 ml of 1/15 M phosphate buffered saline (pH 7.4) was added to the microemulsion, thus giving a 1% injectable preparation, to which an aqueous medium was added according to intended use.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity and particle size, and the results are give in Table 2.

Examples 9-12

Injectable preparations of Examples 9 to 12 were prepared according to the same procedure as in Examples 5-8, except for use of a 20% trehalose solution as an aqueous medium.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity and particle size, and the results are given in Table 2.

Examples 13-16

Injectable preparations of Examples 13 to 16 were prepared according to the same procedure as Examples 5-8, except for use of 10 ml of a 10% trehalose solution as aqueous medium.

Using conventional methods known in the art, the resulting injectable preparation was analyzed for optical clarity and particle size, and the results are given in Table 2.

Table 2. Optical clarity and particle sizes of injectable preparations of Examples 5-16		
Injectable Preparation	Optical clarity (%, at 660 nm)	Particle size (nm)
Example 5	99.16	26.2
Example 6	98.95	25.5
Example 7	99.38	24.6
Example 8	98.75	26.0
Example 9	100.00	33.6
Example 10	99.83	34.3
Example 11	99.74	29.7
Example 12	99.03	34.2
Example 13	98.71	29.1
Example 14	99.57	27.6
Example 15	98.92	25.2
Example 16	99.14	25.6

Example 17-19

According to Table 3, phosphate buffered saline (pH 7.4) was used as an aqueous medium in Example 17, a 10% trehalose solution was used in Example 18, and distilled water for injection was used in Example 19. An oil-phase solution in each of Experiments 17-19 was prepared according to the procedure of Example 7. A 1% injectable preparation in each of Examples 17-19 was prepared according to the procedure of Example 1 except that a final volume of 120 ml was obtained.

Table 3. Compositions of injectable preparations of Examples 17 to 19			
	Example 17	Example 18	Example 19
Aqueous solutions	50 ml PBS	50 ml 10% trehalose	50 ml distilled water
	7.5 g Solutol	7.5 g Solutol	7.5 g Solutol
Oil-phase solutions	15 g Glycofurol	15 g Glycofurol	15 g Glycofurol
	250 mg SDC	250 mg SDC	250 mg SDC
	500 mg 99% egg lecithin	500 mg 99% egg lecithin	500 mg 99% egg lecithin
	1.2 g propofol	1.2 g propofol	1.2 g propofol
PBS	q.s.	q.s.	q.s.
Total Volume	120 ml	120 ml	120 ml

Using conventional methods known in the art, the resulting injectable preparations were analyzed for pH, optical clarity, viscosity, and particle size, and the results are given in Table 4.

Table 4				
Injectable Preparation	pH	Optical Clarity at 660 nm (%)	Viscosity (cp)	Particle size (nm)
Example 17	7.6	98.7	0.8747	26.5
Example 18	7.4	97.9	0.8764	27.1
Example 19	7.5	99.0	0.8705	23.2

Example 20

According to Table 5, a dextrose solution was used as an aqueous medium instead of trehalose solution, and an oil-phase solution was prepared by reducing an amount of egg lecithin to 250 mg and adding 1.1 g of the drug propofol. In each Example, a 1% injectable preparation was formulated according to procedure of Example 1 except that a final volume of 110 ml was

obtained.

Table 5. Compositions of injectable preparations			
	Example 17	Example 18	Example 19
Aqueous solutions	50 ml distilled water	50 ml 10% dextrose	50 ml 10% dextrose
	7.5 g Solutol	7.5 g Solutol	7.5 g Solutol
Oil-phase solutions	15 g Glycofurol	15 g Glycofurol	15 g Glycofurol
	250 mg SDC	250 mg SDC	250 mg SDC
	250 mg 99% egg lecithin	250 mg 99% egg lecithin	250 mg 99% egg lecithin
	1.1 g propofol	1.1 g propofol	1.1 g propofol
PBS	q.s.	q.s.	q.s.
Total Volume	110 ml	110 ml	110 ml

Using conventional methods known in the art, the resulting injectable preparations were analyzed for pH and optical clarity, and the results are give in Table 6.

Table 6		
Injectable Preparation	pH	Optical Clarity at 660 nm (%)
Example 17	7.5	96.04
Example 18	6.7	94.93
Example 19	6.9	97.24

Experimental Example 1

Test for an anesthetic effect of the injectable preparation. The injectable preparation of Example 5 was compared with the oil-based emulsion DIPRIVAN in terms of anesthetic effect according to their administered amounts, as well as on blood pressure and respiration in rabbits.

Three rabbits of about 3 kg of body weight were used in each case. After immobilizing rabbits on a fixed board, a 24-ga. venous catheter was inserted into the ear vein, and an anesthetic agent was injected into the ear vein through the catheter. After recording baseline levels of the venous pressure at the rabbit ear, the anesthetic agent was injected at a rate of 1 ml/kg/hr. After 10 minutes, the venous pressure at the rabbit ear was again recorded. Thereafter, the injected amount of the anesthetic agent was increased to 2 ml/kg/hr, 4 ml/kg/hr, 6 ml/kg/hr, 8 ml/kg/hr, and 10 ml/kg/hr at intervals of 10 minutes.

The anesthetic effect of the treatment was evaluated by inserting a 24-gauge arterial catheter into the ear artery, and the arterial pressure at the rabbit ear was measured. Induction of anesthesia in rabbits was evaluated by stimulating the cornea with gauze, or investigating response of the end of the rabbit's nose upon being pricked with a needle, which is the so-called pinprick stimulation method.

The results are give in Tables 7 and 8.

Table 7. Effect of the injectable preparation of Example 5 on induction of anesthesia in rabbits.

	Rabbit No.	Baseline	Dose rate (ml/kg/hr)					
			1	2	4	6	8	10
BP (S/D)	1	105/70	105/71	95/70	79/61	73/61	61/47	68/48
	2	100/65	94/61	89/60	80/70	74/65	71/62	69/58
	3	100/70	92/64	90/65	87/65	107/83	87/62	83/53
Stimulation of the cornea	1	+++	+++	+++	+	+	+	+
	2	+++	+++	+++	++	+	+	+
	3	+++	+++	+++	++	++	+	+
Pinprick stimulation	1	+++	+++	+++	+	+	+	+
	2	+++	+++	+++	++	+	+	+
	3	+++	+++	+++	++	+	±	-
Difficulty in breathing	1	-	-	-	-	-	-	+
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-

Table 8. Effect of DIPRIVAN on induction of anesthesia in rabbits								
	Rabbit No.	Baseline	Dose rate (ml/kg/hr)					
			1	2	4	6	8	10
BP (S/D)	4	79/61	82/65	83/64	65/52	84/63	84/60	81/61
	5	100/66	110/69	92/70	85/73	82/66	anes-thetized	death
	6	91/63	85/63	83/60	60/54	63/57	70/59	70/59
Stimu-lation of the cornea	4	+++	+++	+++	+++	+	+	±
	5	+++	+++	+++	+++	+++	-	-
	6	+++	+++	++	+	+	+	±
Pinprick stimula-tion	4	+++	+++	+++	++	+	+	±
	5	+++	+++	+++	+++	+++	-	-
	6	+++	+++	++	+	+	+	±
Difficulty in breathing	4	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	death
	6	-	-	-	-	-	-	-

As is apparent from the data in Tables 7 and 8, the injectable preparation of Example 5 has an anesthetic effect similar to that of DIPRIVAN.

Experimental Example 2

Assay for stability of the injectable formulations of Examples 5 to 16. After being kept in cold storage for 90 days, the injectable preparations of Examples 5 to 16 were analyzed for stability using HPLC. The pump was a Waters model 510, and the detector was a Waters model 486. The column was an Intersil ODS 3.5 μm, 4.6 x 250 mm from GL Science. The mobile phase was acetonitrile:water:acetic acid (pH 2.0) in a ratio of 70:30:0.1. The sample size injected was 50 μl, and fractionation was carried out at a flow rate of 1.2 ml/min. Detection was at 276

nm.

The results of these HPLC assays showed that all of the formulations had stabilities in the range of 98 to 100%.